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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/014,326	11/13/2001	Bent Karsten Jakobsen	102286.409CON	5062

7590 12/27/2004

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 12/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/014,326	JAKOBSEN ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22 and 25-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22, 25-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant cancels claims 23-24, and adds new claim 35, which is related to claims 22-34 and is not new matter.

Accordingly, claims 22, 25-35 are being examined.

The following are the remaining rejections.

SUBSTITUTE SPECIFICATION

The submission of the substitute specification for correction of clerical errors is acknowledged and entered.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

Claim 33 remains rejected under 35 USC 112, first paragraph, pertaining to lack of enablement for a soluble T cell receptor linked to "a therapeutic agent", for reasons already of record of paper of 04/09/04.

New claim 35 is rejected for the same reasons already of record.

Applicant argues that there is no basis for the Office action to contend that a therapeutic agent that has been shown to be effective in untargeted form will not be effective when targeted by virtue of being attached to a soluble TCR of the invention.

Applicant's arguments in paper of 10/12/04 have been considered but are found not to be persuasive for the following reasons:

Although therapeutic agent has been shown to be effective when conjugated to an effective carrier, one cannot predict that said therapeutic agent is effective when conjugated to the claimed soluble TCR, in view of the unpredictability of the effectiveness of the claimed soluble TCR as an effective carrier for treating for delivering a therapeutic agent, which is a cytotoxic compound or an immunostimulating compound to target cells presenting a particular antigen, as contemplated (specification, page 7, second paragraph, p.17), and in view that treating diseases, including the contemplated cancer treatment, as taught by Gura et al, Jain et al, Curti et al, Hartwell et al, all of record. It is well known in the art that a therapeutic agent must accomplish several tasks to be effective. It must be delivered into the circulation that supplies the target cells and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. Further, variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The soluble TCR may be inactivated *in vivo* before producing a sufficient effect, for example, by proteolytic degradation, immunological activation or due to an inherently short half life of the protein and the *in vitro* tests of record do not sufficiently duplicate the conditions which occur *in vivo*. In addition, the soluble TCR may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the soluble TCR has no effect, circulation into the target area may be insufficient to carry the soluble TCR and a large enough local concentration may not be established.

REJECTION UNDER 35 USC 103

1. Claims 22-27, 29, 34 remain rejected under 35 USC 103(a) as being obvious over Chang et al, 1994, Proc Natl Acad Sci, USA, 91: 11408-11412, IDS of 03/25/02, in view of Gregoire et al, 1991, supra, Garboczi et al, 1996, J Immunol, 157(12): 5403-10, IDS of 03/25/02, and Wulfing et al, 1994, J Mol Biol, 242: 655-669, for reasons already of record in paper of 04/09/04.

A. Applicant argues that Gregoire et al use a pair of immunoglobulin Ck domains as dimerization domains, which present particular problems of quaternary structure, because the –NH2 termini must be spaced far apart, and therefore, when using Ck domains, the portion of each TCR C-alpha and C-beta domain encoded by exon 2 should be deleted. Applicant argues that given the large structural differences in the constructs of Gregoire et al and Chang et al, and therefore, there is no motivation to combine the teaching of the references.

Applicant argues that one does not know whether the chimeric construct taught by Gregoire et al can be functional, because no binding data is provided for the construct. Applicant argues that the reference does not demonstrate that removal of the disulfide bond encoded in exon 2 of the C-alpha and C-beta chain results in correct TCR alpha and beta pairing. Applicant concludes that therefore, the reference does not provide any teaching or suggestion as to what effect of removal of the interchain disulfide bond from Chang construct will have.

Applicant argues that Gregoire et al is published in 1991 and was available to Chang et al, yet Chang et al did not attempt to make the construct without an interchain disulfide bond.

Applicant's arguments of 10/12/04 have been considered, but are found not to be persuasive for the following reasons:

It is noted that regardless of why the portion of each TCR C-alpha and C-beta domain encoded by exon 2 should be deleted in the construct taught by Gregoire et al, the teaching of Gregoire et al that the unique ability of their construction to form alpha-k-beta-k dimers may be due the lack of the cysteine residue located at the COOH-terminal to the end of the C alpha and C beta regions (p.8080, second column, first paragraph) clearly indicates that the lack of disulfide bond located at the C-terminal end of the C alpha and beta regions facilitates the dimerization process of the dimerizing domains, i.e. the cysteine residue located at the COOH- terminal of TRC is a hindrance for the dimerization process.

Further, although Gregoire et al is published in 1991 and was available to Chang et al, and although Chang et al did not attempt to make the construct without an interchain disulfide bond, it is noted that this defect is cured by the teaching of Garboczi et al. Further Chang et al is recited to show that leucine zipper is an effective, preferred dimerizing domain for TCR, and it is noted in a 103 rejection, a cited reference does not have to teach all aspects of the claimed invention.

B. Applicant argues that the coiled coil domains in the reference by Wulfing et al are not used to hold together the alpha and beta chains, but rather to associate the

respective single chains alpha and beta, and that the coiled coil domain forms a homodimer. Applicant argues that Wulfing et al teach that the chains must be associated covalently, teaching towards the inclusion of the native disulfide bond, and teaching away from the present invention.

Applicant's arguments of 10/12/04 have been considered, but are found not to be persuasive for the following reasons:

It is noted that the reference by Wulfing et al is not cited for the teaching of their construct per se. Rather, Wulfing et al is cited because Wulfing et al teach that the correctly folded scTCR is essentially stable, whereas misfolded scTCR is rapidly degraded, and that the effect of increased yields in the direct over-expression system is due to enhanced in vivo folding, working synergistically with substantially higher intrinsic proteolytic stability of the correctly folded material (p.665, second column, last two paragraph, bridging p. 666). This teaching is true, and would be applicable to any TCR construct, regardless what type of TCR construct is used.

From the teaching of Wulfing et al one would have expected that higher yields of TCRs are correlated with correct TCR folding, and thus a decrease in the yield of alpha and beta chains of TCR expressed with the interchain disulfide bonds, as compared to alpha and beta chains of TCR expressed without the interchain disulfide bonds as taught by Garboczi et al, indicates an increase in misfolding of alpha and beta chains of TCR expressed with the interchain disulfide bonds. In other words, the interchain disulfide bond seems to interfere with the folding of the alpha and beta chains of TCRs.

Thus **from the teaching of Garboczi et al (see discussion below) and Wulfing et al, one of ordinary skill in the art would expect that the interchain disulfide bond of TCR not only is not necessarily for TCR binding to the target peptide, but also could interfere with the folding of the alpha and beta chains, resulting in lower yield**.

C. Applicant asserts that the Office action allegation that Garboczi et al teach that "heterodimerization and antigenic specificity of TCR do not require its interchain disulfide bond" is not supported by the experiments described in this paper. Applicant asserts that rather the TCR heterodimers produced by the method of Garboczi et al require disulfide bond.

Applicant asserts that specifically in figure 2B, in none of the six lanes of the gel were the iodoacetamic-treated alpha and beta subunits tested for heterodimer formation in the absence of the stabilizing MHC molecule and an MHC-binding peptide. Applicant asserts that the only lane (lane 6) which includes both the alpha and beta subunits also include the MHC molecule (HLA-A2) and the MHC-binding protein (Tax) which help to stabilize the heterodimer. Applicant concludes that therefore, these experiments do not demonstrate that the alpha and beta subunits of Garboczi et al form a heterodimer absent the interchain disulfide bond.

Applicant further asserts that in figure 3, under reducing conditions, which eliminates the interchain disulfide bond, the 60 kDa TCR heterodimer dissociates into its constituent about 29 kDa chains. Applicant asserts that these experiments suggest that the disulfide bond of Garboczi et al is necessary for heterodimer formation.

Applicant asserts that in figure 4, in both lanes, no alpha-beta TCR heterodimers are formed, but rather the alpha and beta subunits form distinct bands.

Applicant's arguments of 10/12/04 have been considered, but are found not to be persuasive for the following reasons:

Contrary to Applicant's arguments, Garboczi et al clearly teach that "heterodimerization and antigenic specificity of TCR do not require its interchain disulfide bond", as shown not only in the text, but also in the disclosed figures.

Garboczi et al concludes from the experiments using the long form, full length TCR (figures 2-3 on p. 5406), that the TCR-alpha-beta lacking the interchain disulfide bond still bound to HLA-A2/Tax (p.5405, second column, paragraph under "Specific binding of alpha beta heterodimers to HLA-A2/Tax using a band-shift assay" bridging p.5406). Further, based on said knowledge from figure 2B, Garboczi et al go on and teach that , using truncated soluble TCR, without the C-terminal-most cysteines, alpha and beta associate without an interchain disulfide bond and bind specifically to HLA-A2/Tax (figure 4 on p. 5407, and p.5406, second column, under "Alpha and beta associate without an interchain disulfide bond and bind specifically to HLA-A2/Tax" bridging p.5407).

Applicant interpretation of the data of the "native" gel in figure 2B and SDS gel of figure 3 misrepresents the purposes of figures 2-3 . As interpreted by Garboczi et al, figure 2B shows that the TCR-alpha-beta lacking the interchain disulfide bond still bound to HLA-A2/Tax , and that neither the alpha nor the beta subunit alone binds to HLA-A2/Tax (p.5406, first column, last paragraph, bridging second column). In figure

2B, lanes 1-5 are control lanes. Lane 1 is the control of HLA-A2/Tax alone. Lanes 2-3 are alpha subunit or beta subunit alone. Lanes 4-5 show non-binding of either the alpha or beta subunit alone to HLA-A2/Tax. Lane 6 shows binding of the TCR alpha-beta heterodimer to HLA-A2/Tax, even in the presence of iodoacetamide, which blocks the interchain disulfide formation. Thus in lanes 2-5, no heterodimer of alpha and beta is formed, because the alpha and beta subunit are run alone, without each other. Further, the data on lane 6, in which the full length alpha and beta form dimerization in the absence of interchain disulfide, and in the presence of HLA-A2/Tax, indicates that the full length alpha and beta form dimerization in the absence of interchain disulfide (p.5406, first column, second paragraph, bridging second column), which is further confirmed by the experiment recited on pages 5406-5407 of Garboczi et al (see discussion below, on page 9 of this Office action, last two paragraphs, bridging p.10).

Moreover, the argument by Applicant that HLA-A2/Tax stabilizes, i.e. is required for, the dimerization of the alpha and beta TCR chain in the absence of interchain disulfide bond, is contradictory to the experiment on recited on pages 5406-5407 of Garboczi et al (see discussion below, on page 9 of this Office action, last two paragraphs, bridging p.10).

Further, the denaturing SDS-PAGE gel in figure 3 confirms that the TCR complex in lanes 1, 2 of figure 2A under native gel is the complex of full length TCR-alpha-beta-HLA-A2/Tax (p.5405, second column, fourth paragraph), because under denaturing SDS-PAGE gel in figure 3, it could be separated into the three components, whole apha-beta TCR, HLA-A2 and Tax, under non reducing condition (lane 1 of figure 3),

wherein under which condition, the interchain disulfide bond is present in TCR. Under reducing conditions, where the interchain disulfide bond is absent in TCR, TCR is shown to be dissociated into alpha and beta chains (lane 2 of figure 3).

In addition, the non-covalent association of alpha and beta without an interchain disulfide bond is clearly confirmed by the next experiment by Garboczi et al " (figure 4 on p. 5407, and p.5406, second column, under "Alpha and beta associate without an interchain disulfide bond and bind specifically to HLA-A2/Tax" bridging p.5407).

In this experiment, the shortened form of TCR without the C-terminal-most cysteine is used. Garboczi et al teach that shortened alpha and beta subunits refold and heterodimerize by rapid dilution of the mixture of said alpha and beta subunits (p.5407, second column, last paragraph). The refolded heterodimer, which is non-covalent linked together without the C-terminal-most cysteine is purified from gel filtration chromatograph as a 40 kDa protein (p.5407, first column, first paragraph). Garboczi et al go on and teach that the refolded non-covalent associated shortened TCR without the C-terminal-most cysteine is stable and very soluble and is routinely prepared (p.5047, first column, paragraph before last). This purified heterodimer is subjected to denatured SDS-PAGE of figure 4, which confirms that the purified heterodimer is dissociated into beta and alpha chains under denatured SDS-PAGE, with either reduced or non reduced condition, wherein under non-reducing conditions the formation of "intrachain" disulfide of the individual subunits causes a more compact structure and thus a difference in mobility in SDS-PAGE, as compared to that of the reduced condition (figure 4 legend in p.5407). It is noted that different from full length TCR, in which the

alpha and beta chains are covalently linked by the interchain disulfide bond, non-covalent linked peptides would be dissociated under SDS-PAGE. It is further noted that the shortened alpha and beta chain still contain cysteines that naturally form intrachain disulfide bonds as shown in the figure 2A on page 11410 in the reference by Chang et al.

Thus this experiment on pages 5406-5407 of Garboczi et al, and the interpretation by Garboczi et al clearly demonstrate that alpha and beta TCR chains associate without an interchain disulfide bond, and without the presence of the MHC molecule, and contradict Applicant's interpretation that the disulfide bond of Garboczi et al is necessary for heterodimer formation.

D. In addition, Applicant argues that in figure 5A, lanes 2, 4, 6, 8, wherein alpha or beta chains are run alone, no alpha-beta heterodimers are formed, and that in lanes 3, 5, 7, and 9, wherein the HLA-2/Tax are present with the alpha and beta subunits, the HLA-2/Tax-TCR alpha-beta complex is formed. Applicant concludes that the HLA-A2/Tax is necessary to stablize the heterodimers between the TCR alpha and beta chains. Applicant argues that in figure 5B and C, without the MHC molecule and the MHC-binding peptide, no alpha-beta heterodimer is formed. Applicant concludes that the results suggest that the alpha and beta TCR subunits do not form heterodimer without interchain disulfide bonds, except when held in complex with an MHC molecule and MHC-binding peptide.

Applicant's arguments of 10/12/04 have been considered, but are found not to be persuasive for the following reasons:

Applicant interpretation of the data of in figure 5 misrepresents the purposes of figure 5, which shows that noncovalently associated TCR-alpha-beta forms a complex with HLA-A2/Tax (see figure 5 legend on page 5407, and p. 5407, under "Interaction of TCR with altered peptide ligand" , bridging p.5408).

Further, as shown by the experiment on pages 5406-5407 of Garboczi et al, supra, a simple dilution of a mixture of the shortened alpha and beta subunits, which do not have the C-terminal-most cysteines, results in heterodimerization of said subunits, as taught by Garboczi et al, and thus the alpha and beta subunits seem to form a stable complex in the absence of both the disulfide interchain bond and the HLA-A2/Tax, since there is no mentioning in the experiment by Garboczi et al that HLA-A2/Tax is present in said mixture. **Thus the HLA-A2/Tax does not seem to be required for the formation of the stable noncovalent alpha-beta heterodimer, without the disulfide interchain bond, in view of the teaching of Garboczi et al.**

Applicant concludes that because of the above reasons, there is no motivation provided by the teaching of Garboczi et al to modify the soluble TCRs of Chang et al by removing the interchain disulfide bonds, and that Garboczi et al teach away from the invention.

Applicant's arguments of 10/12/04 have been considered, but are found not to be persuasive for the following reasons:

Contrary to Applicant's arguments, Garboczi et al do not teach away from the invention, for reasons set forth above.

Further Garboczi et al teach that the alpha and beta chains of TCR, without the interchain disulfide bonds, when refolded together, form heterodimers spontaneously and at higher yield than the alpha and beta chains of TCR expressed with the interchain disulfide bonds (p.5404, first column, second paragraph).

Thus Garboczi et al provide motivation to modify the soluble TCRs of Chang et al by removing the interchain disulfide bonds, i.e. the alpha and beta chains of TCR, without the interchain disulfide bonds, when refolded together, form heterodimers spontaneously and at higher yield than the alpha and beta chains of TCR expressed with the interchain disulfide bonds.

E. Applicant further argues that although Chang et al construct ensures strong association between the two chains, by the coiled-coil dimerization, and the presence of native interchain disulfide, Chang et al do not demonstrate specific binding to the peptide-MHC complex. Applicant argues that hence it is impossible to infer from Chang et al the effect of omitting the native disulfide bridge on peptide-MHC binding. Applicant argues that this effect of the omission is not cured by Garboczi et al, because one does not know from either Chang et al, or Garboczi et al the contribution made by the coiled –coil interactions alone to the conformation of the heterodimers, and thus its specific binding functionality.

Applicant's arguments of 10/12/04 have been considered, but are found not to be persuasive for the following reasons:

It is noted that Gregoire et al teach that the structure of TCR is closely related to immunoglobulinl, with the TCR V alpha and V beta chains positioned similar to the

immunoglobulin complementary determining regions (CDR) in an Fab-like model similar to antibody, for recognition of MHC/peptide ligand (p.8077, first column, first paragraph).

It is further noted that omission of the native disulfide bridge does not effect the binding of the alpha- beta TCR heterodimer to the peptide-MHC, as shown by Garboczi et al, supra (Garboczi et al, p. 5407, under "Interaction of TCR with altered peptide ligand" , bridging p.5408).

Further, fusion of the full length TCR heterodimer to the leucine zipper does not effect the structure of the TCR, as taught by Chang et al (abstract).

Similarly, leucine zipper has been routinely used in the art for dimerizing compounds, such as Fab, without effecting the binding of the Fab fragment to its antigen, as taught by US 5,582, 996.

In addition, Chang et al teach that the leucine zipper dimerizing domains are attached to the C terminal of the TCR (figure 2 on page 11410), and one would have expected that the C-terminus is not the recognition site for antigen necessary for the action of the TCR, and thus addition of at the C-terminus of the soluble TCR alpha and beta chains would be least likely to interfere with antigen binding.

Thus, one would have expected that more likely than not, similar to the full length TCR heterodimer taught by Chang et al, and the Fab fragment taught by US 5,582, 996, the structure of the truncated alpha- beta TCR heterodimer, without C-terminal most cysteines, would not be effected by leucine zipper, and thus its binding ability to the peptide-MHC.

F. Concerning the amendment of claim 22 to read on a recombinant soluble T cell receptor (TCR), wherein the TCR is capable of specific binding to a peptide-MHC complex at a concentration of at least 40 ug/ml, it is noted that the soluble TCR taught by the combined references seems to be the same as the claimed soluble TCR, and thus one would have expected that it has the same properties and characteristics.

Although the reference does not specifically teach that the TCR is capable of specific binding to a peptide-MHC complex at a concentration of at least 40 ug/ml, however, the claimed TCR appears to be the same as the prior art TCR, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable diffrences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

2. Claim 28 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al, 1994, supra, in view of Gregoire et al, 1991, supra, Garboczi et al, 1996, J Immunol, 157(12): 5403-10, IDS of 03/25/02, and and Wulfing et al, 1994, J Mol Biol, 242: 655-669 as applied to claims 22-27, 29, 34 above, and further in view of US 5,643,731 or US 5,582,996, for reasons already of record in paper of 04/09/04.

Applicant argues that since Chang et al, in view of Gregoire et al, Garboczi et al and Wulfing et al do not render obvious the claimed invention, and since neither US

5,643,731 nor US 5,582,996 cures the deficiencies of these references, the rejection should be withdrawn.

Applicant's arguments in paper of have been considered but are found not to be persuasive for the following reasons:

Rejection remains, because Chang et al, in view of Gregoire et al, Garboczi et al and Wulfing et al render obvious the claimed invention, *supra*.

Therefore, it would have been obvious to use the c-jun and v-fos peptides taught by US 5,643,731 or US 5,582,996, as dimerizing peptides for the construct taught by the combination of Chang et al, Gregoire et al, Garboczi et al and Wulfing et al, because they are the preferred dimerizing peptides, as taught by US 5,643,731, and because the c-jun and v-fos peptides have been successfully used for dimerizing antibody Fab fragment, with retention of antigen binding property, as taught by US 5,582,996.

3. Claim 30 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al, 1994, supra, in view of Gregoire et al, 1991, supra, Garboczi et al, 1996, J Immunol, 157(12): 5403-10, IDS of 03/25/02, and and Wulfing et al, 1994, J Mol Biol, 242: 655-669 as applied to claims 22-27, 29, 34 above, and further in view of Arcone, R, 1991, Eur J biochem, 198(3): 541-7 , for reasons already of record in paper of 04/09/04.

Applicant argues that since Chang et al, in view of Gregoire et al, Garboczi et al and Wulfing et al do not render obvious the claimed invention, and since Arcone et al do not cure the deficiencies of these references, the rejection should be withdrawn.

Applicant's arguments in paper of have been considered but are found not to be persuasive for the following reasons:

Rejection remains, because Chang et al, in view of Gregoire et al, Garboczi et al and Wulfing et al render obvious the claimed invention, *supra*.

It would have been obvious to express in E. coli the construct taught by the combination of Chang et al, Gregoire et al, Garboczi et al and Wulfing et al, because the E. coli expression system provides a high yield as taught by Arcone et al, and because it is well known in the art that E. coli system is easy to handle and grow quickly in large quantity.

4. Claims 31-32 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al, 1994, supra, in view of Gregoire et al, 1991, supra, Garboczi et al, 1996, J Immunol, 157(12): 5403-10, IDS of 03/25/02, and Wulfing et al, 1994, J Mol Biol, 242: 655-669 as applied to claims 22-27, 29, 34 above, and further in view of US 5,635,363, for reasons already of record in paper of 04/09/04.

Applicant argues that since Chang et al, in view of Gregoire et al, Garboczi et al and Wulfing et al do not render obvious the claimed invention, and since US 5,635,363 does not cure the deficiencies of these references, the rejection should be withdrawn.

Applicant's arguments in paper of have been considered but are found not to be persuasive for the following reasons:

Rejection remains, because Chang et al, in view of Gregoire et al, Garboczi et al and Wulfing et al render obvious the claimed invention, *supra*.

It would have been obvious to biotinylate and label the construct taught by the combination of Chang et al, Gregoire et al, Garboczi et al and Wulfing et al, using the method taught by US 5,635,363 to detect said construct.

Moreover, it would have been obvious to biotinylate said soluble TCR at the C-terminus, because one would have expected that the C-terminus is not the site where the alpha and beta chains are, which contain the recognition site for antigen necessary for the action of the TCR, and thus biotinylation at the C-terminus would be least likely to interfere with antigen binding, as compared to biotinylation at the N-terminus.

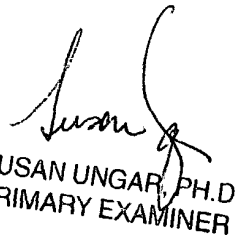
THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



MINH TAM DAVIS

December 13, 2004